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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/833,745	04/13/2001	Joseph Roberts	78728/106	2894

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EXAMINER
PATTERSON, CHARLES L JR

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/833,745	ROBERTS ET AL.	
	Examiner	Art Unit	
	Charles L. Patterson, Jr.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004 and 18 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/18/04 has been entered.

The statement the examiner made in the last action that it "is not understood...[how] SEQ ID NO:13 and 14 [could] have 30 and 24 residues...[when] the 'coordinates' in Table 1 are 838-867 and 1370-1393" was apparently incorrect. The indicated regions are 30 and 24 residues, respectively. This error by the examiner is regretted.

The amendment filed 1/20/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is Figure 8 and the recitation on SEQ ID NOS: 7 or 12" in the legend to Table 1..

Figure 8, as filed in the instant application, was a blank box labeled at the top "Figure 8: Effect of pH on HAL". Applicants have now submitted the figure that was apparently filed in the provisional application (60/197,770). However, the examiner can find no specific incorporation of the provisional application into this application, only a statement that the priority of it is claimed, and therefore its inclusion in this application is new matter and must be deleted absent a convincing argument that it has been specifically incorporated into this application. In addition, applicants must renumber all of the figures to eliminate Figure 8, since to not do this

would make the application confusing, and remove all references to the figure in the specification. The only references to the contents of the figure that the examiner can find in the instant specification are paragraph 34, which simply repeats the information in the title to the figure, and paragraph 146, where it is stated that "[t]he enzyme is active over a wide range of pH, with the highest activity around pH 8.2 and high activity in physiological conditions". The figure submitted has two peaks of activity at around pH 8.0 and 9.0, with a broad peak from about pH 8.0 to 9.0. Therefore, the specification does not describe the figure sufficiently such that it may be added to the application at this stage.

Applicants have given no reason as to why the phrase "on SEQ ID NOS: 7 or 12" was added to the legend to Table 1 and it is not readily apparent. Absent some other teaching of this in the specification as filed, it is objected to as new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claim is confusing in the recitation of "and-the" in line 3. Apparently the hyphen should be deleted.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to methods of treatment of a patient. The specification teaches *in vitro* experiments using cell cultures. There is no correlation shown between these *in vitro* methods and actual treatment of a patient. A patient, whether it be human or some other organism, has a myriad of enzymes, hormones, etc. working together. Without some indication that the methods of the instant claims would be effective when administered to patients, one of ordinary skill in the art would not believe that applicants had actually treated patients. In addition, the method of claims 13-15 for reducing toxicity to normal cells from chemotherapeutic agents or retroviral vectors and the method of claims 16-20 for delivering an immunosuppressant to a patient is not shown in the specification to work for even *in vitro* treatments, absent very convincing proof to the contrary.

Claims 7-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As discussed *supra*, the instant specification only discloses the use of cultured cells *in vitro* to test the enzyme HAL. Nothing is taught about the

actual treatment of patients and it is maintained that without some such teaching, one of ordinary skill in the art could not use the instant method to treat patients. Patients have a vast numbers of interacting substances and systems operating together and without some teaching that some particular method of administering the enzyme, at some specific concentration, with or without some other substance administered along with it, by a particular means such as oral, venous, liposomes, etc. would be operable and not perhaps harmful, one of ordinary skill in the art would not know how to use the instant claimed invention. In addition, as discussed *supra*, the method of claims 13-15 for reducing toxicity to normal cells from chemotherapeutic agents or retroviral vectors and the method of claims 16-20 for delivering an immunosuppressant to a patient is not shown in the specification to work for even *in vitro* treatments, absent very convincing proof to the contrary.

As has been discussed previously, claims 8 and 12 are drawn to histidine ammonia lyases from *Corynebacteriaceae* having conservative substitutions and are thus not enabled. Applicants argue that the "specification discloses sequence variations that are contemplated by the invention" but the effect of these variations are now shown. They further state that "[o]ne of skill in the art would understand how to make and use these variants in accordance with the claimed method...[and] are enabled by the specification. It is agreed that one of ordinary skill in the art would understand how to make these variants but the effect these changes is not taught in the specification and therefore this artisan would not have been taught how to use the variants. What effect any change in the sequence of an enzyme will have is not readily predictable and therefore such conservative substitutions are not taught by the specification. The substitutions could cause a loss in activity or change the activity to something undesirable to the patient.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by either of Roberts, et al. (A1) or Jack, et al. (A5).

The instant references teach administering a histidine ammonia lyase to a patient to treat carcinoma, sarcoma and leukemia. The instant claim is drawn to a method of treatment comprising administering a histidine ammonia lyase. The claim states that the patient is "suffering from a viral infection" but the claim does not state that the purpose of administering the enzyme is to treat this viral infection. The motivation would have been to treat a carcinoma or leukemia that the patient may be suffering from.

Claims 8-9 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts, et al. (A1) in view of either of Brand, et al. (B2) or Rechler (U). Roberts, et al. teaches the histidine ammonia lyase (histidase) of the instant claims, absent very convincing proof to the contrary. The re-

ference also teaches that the enzyme may be used to treat carcinoma or sarcoma. Brand, et al. and Rechler teach methods of purifying the enzyme to 1910 units/mg and 66,700 units/mg, respectively. It would have been obvious to one of ordinary skill in the art to use the enzyme taught by Roberts, et al. in a treatment method and to purify the histidase using the methods of either of the secondary references, absent unexpected results. The motivation would have been to use a more pure enzyme in the treatment schemes.

The instant claims contain a purity requirement of 40 IU/mg and state that the enzyme activity "is not decreased in the presence of L-histidinol or a therapeutic salt thereof and...corresponds in sequence to histidine ammonia lyase of *Corynebacteriaceae*. As stated *supra*, the enzyme taught by Roberts, et al. from *Corynebacteriaceae* is apparently the same enzyme and therefore has the sequence and L-histidinol requirements of the instant claims. Roberts, et al. also teach a treatment method for carcinomas and sarcomas. As stated *supra*, claim 7 from which claim 8 depends, states that the patient is "suffering from a viral infection" but the claim does not state that the purpose of administering the enzyme is to treat this viral infection. Therefore claims 8-9 and 11 are included in this rejection as they do not include anything that would not have been obvious to do because of the lack of histidinol inhibition. Claim 10 is drawn to also adding histidinol and was not included in this rejection. The secondary references teach methods of purification of the enzyme that obtain a purity much greater than 40 IU/mg and it is maintained that these methods could have been used to purify the enzyme of the instant claims, absent very convincing proof to the contrary. It is further maintained that to increase the purity of an enzyme is always obvious. Further, there are other methods of purification taught for this enzyme which could have been used and also other methods of purification for enzymes in

general that are taught by many other reference and are well known to those of ordinary skill in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 571-272-0936. The examiner can normally be reached on Monday - Friday from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
March 19, 2004